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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,584	09/27/2006	Bruno Mougin	129432	8064

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
07/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,584	MOUGIN ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to paper filed 4/15/2009.

The claims have not been amended.

This action is FINAL.

Claim Rejections - 35 USC § 103-Maintained

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maestro et al (Genes & Development (1999) volume 13, pages 2207-2217), Rosivatz et al (American Journal of pathology (2002) volume 161, pages 1881-1891), Martin et al (Breast Cancer research and Treatment(2003) volume 82, pages S117-s118, abstract 480) and Brodeur (nature Reviews Cancer (2003) volume 3, pages 203-216).

Claim 13 is drawn to a method of prognosing neuroblastoma comprising analyzing Twist expression in a neuroblastoma sample from a patient and comparing Twist expression to Twist expression in a patient with good prognosis and basing prognosis at least in part on Twist expression.

Maestro et al teaches, "A defining characteristic of tumor cells is the escape from regulatory mechanisms that normally restrain cell proliferation. This is accomplished through the accumulation of multiple genetic alterations. Among these are the inactivation of key tumor suppression pathways and the activation of oncogenes" (page 2207, 1st column, 1st paragraph). Maestro teaches that Twist was identified as a gene that inhibited cell death (apoptosis) (page 2209, 1st column, 3rd full paragraph). Maestro teaches that over expression of Twist inhibited cell death in response to serum starvation page 2209, 2nd column, 2nd full paragraph). Maestro teaches Twist antagonizes p53 induced growth arrest and apoptosis.

Rosivatz et al teaches that epithelial mesenchymal transition (EMT) plays a crucial role during early steps of cancer metastasis (abstract). Rosivatz teaches that Twist is known regulate EMT by its role as a transcription factor through its regulation of N-cadherin (page 1882, 1st column 2nd paragraph). Rosivatz teaches that Twist and N-cadherin are upregulated in diffuse gastric tumors (page 1884, 2nd column, lat paragraph). Rosivatz teaches that abnormal upregulation of expression of Twist in tumors suggests that Twist may play a role in EMT by its upregulation of N-cadherin and repression of E-cadherin (page 1889. 1st column). Rosivatz teaches that Twist plays a role in cancer progression (page 18901, 1st column, 1st paragraph).

Martin teaches that node positive breast cancer subjects had elevated Twist expression relative to node negative tissue.

Brodeur teaches the most important clinical variable in predicting outcome of neuroblastoma is the stage of a disease (page 210, 1st column, last paragraph). Broduer et al further suggests that further prognostic indicators are needed (page 210, 2nd column, first paragraph). Brodeur teaches that gene expression may be used as prognostic indicators (page 211, 2nd column, 1st full paragraph). Broduer concludes, "Genetic and molecular profiling of neuroblastomas using microarray, SAGE or other techniques are likely to be used increasingly to identify genetic signatures of subsets of patients that are predictive of outcome. "

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made combine the use of Twist gene expression analysis with neuroblastoma staging information for prognosis of neuroblastoma. The artisan would have been motivated to use gene expression analysis with neuroblastoma staging information because Brodeur suggests gene expression analysis. The artisan would be motivated to specifically assay Twist gene expression in subjects with good and bad prognosis because Maestro has identified Twist as an inhibitor of apoptosis and Rosivatz has identified the role of Twist in EMT transition thus knowledge of Twist expression would provide information on the regulation or presence of apoptotic pathways and EMT transition and metastasis. Further the artisan would be motivated because Martin teaches that Twist has elevated expression in lymph nodes of breast cancer, suggesting Twist expression is elevated in cancer that has spread. It would

have been obvious to one of skill in the art to assay Twist expression due to its role in inhibiting cell death (thus promoting survival and potentially growth), its role in EMT transition (thus mobility of cells) and the findings that it has been found over expressed in lymph nodes of cancer patients. The artisan would have a reasonable expectation of success as Broduer teaches staging is the best predictor of clinical outcome and the additional gene expression information including Twist expression would provide insight into resistance to apoptosis and EMT that is associated with Twist expression. The artisan is thus combining a known technique for prognosing neuroblastoma with expression analysis of a known gene that has been shown to play a role in cancer and metastasis.

Response to Arguments

The response reviews the teachings of Maestro, Rosivatz, Martin and Brodeur. The response specifically notes that Maestro, Rosivatz, Martin and Brodeur do not teach or suggest twist gene expression is a determinative factor in neuroblastoma prognosis. These arguments have been thoroughly reviewed but are not considered persuasive as the claims merely require a comparison to subjects with a good prognosis and determination of prognosis "based at least in part on the comparison of twist gene expression." The teachings of Maestro and Rosivatz demonstrate that Twist gene expression was known to be involved in process associated with cancer and metastasis, while Martin teaches that increased Twist expression has been identified in metastasis to lymph nodes. Thus the combined teachings of Maestro, Rosivatz, and Martin suggest it would be obvious to use Twist gene expression relative to normal

controls to determine prognosis. Brodeur teaches that staging is the most important clinical value in determining prognosis of neuroblastoma and suggests the use of gene expression as an additional prognostic indicator. Thus is would have been obvious to the artisan to use staging of neuroblastoma in conjunction with twist expression to determine prognosis.

4. Claim14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maestro et al (Genes & Development (1999) volume 13, pages 2207-2217), Rosivatz et al (American Journal of pathology (2002) volume 161, pages 1881-1891), Martin et al (Breast Cancer research and Treatment (2003) volume 82, pages S117-s118, abstract 480) and Sotirou et al (Proceedings National Academy of Sciences USA 2003) volume 100, pages 10393-10398).

Claim 14 is drawn to a method of prognosing breast cancer comprising analyzing Twist expression in a breast cancer sample from a patient and comparing Twist expression to Twist expression in a patient with good prognosis and basing prognosis at least in part on Twist expression.

Maestro et al teaches, "A defining characteristic of tumor cells is the escape from regulatory mechanisms that normally restrain cell proliferation. This is accomplished through the accumulation of multiple genetic alterations. Among these are the inactivation of key tumor suppression pathways and the activation of oncogenes" (page 2207, 1st column, 1st paragraph). Maestro teaches that Twist was identified as a gene that inhibited cell death (apoptosis) (page 2209, 1st column, 3rd full paragraph). Maestro teaches that over expression of Twist inhibited cell death in response to serum

starvation page 2209, 2nd column, 2nd full paragraph). Maestro teaches Twist antagonizes p53 induced growth arrest and apoptosis.

Rosivatz et al teaches that epithelial mesenchymal transition (EMT) plays a crucial role during early steps of cancer metastasis (abstract). Rosivatz teaches that Twist is known regulate EMT by its role as a transcription factor through its regulation of N-cadherin (page 1882, 1st column 2nd paragraph). Rosivatz teaches that Twist and N-cadherin are upregulated in diffuse gastric tumors (page 1884, 2nd column, lat paragraph). Rosivatz teaches that abnormal upregulation of expression of Twist in tumors suggests that Twist may play a role in EMT by its upregulation of N-cadherin and repression of E-cadherin (page 1889. 1st column). Rosivatz teaches that Twist plays a role in cancer progression (page 18901, 1st column, 1st paragraph).

Martin teaches that node positive breast cancer subjects had elevated Twist expression relative to node negative tissue.

Soritou teaches microarray analysis of breast cancer have identified gene expression profiles able to separate tumor classes associate with patient survival (page 10397, 1st column, 2nd full paragraph). Soritou teaches that their report provides evidence for the use of microarray technology and gene expression patterns as a prognostic indicator for breast cancer (page 10397, 1st column, last paragraph). Soritou teaches that a set of 56 genes could function as a bona fide prognostic marker (page 10397, 2nd column, last paragraph).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made combine the use of Twist gene expression

analysis with the gene expression array profiling of Soritou. The artisan would be motivated to specifically assay twist gene expression because Maestro has identified Twist as an inhibitor of apoptosis and Rosivatz has identified the role of Twist in EMT transition. Further the artisan would be motivated because Martin teaches that Twist has elevated expression in lymph nodes of breast cancer, suggesting Twist is increased in breast cancer metastasis. It would have been obvious to one of skill in the to assay Twist expression due to its role in inhibiting cell death (thus promoting survival and potentially growth), its role in EMT transition (thus mobility of cells) and the findings that it has been found over expressed in lymph nodes of patients of other cancer patients. The artisan would have a reasonable expectation of success as Soritou teaches his method of staging by gene expression provides bona fide diagnostic markers and the inclusion of Twist gene expression would add more data. The artisan is thus combining a known technique for prognosing cancer with expression analysis of a known gene that has been shown to play a role in cancer and metastasis.

Response to Arguments

The response reviews the teachings of Maestro, Rosivatz, Martin and Sotiriou. These arguments have been thoroughly reviewed but are not considered persuasive as the claim requires a comparison to subjects with a good prognosis and determination of prognosis "based at least in part on the comparison of twist gene expression." The teachings of Maestro and Rosivatz demonstrate that Twist gene expression was known to be involved in process associated with cancer and metastasis, while Martin teaches that increased Twist expression has been identified in metastasis to lymph nodes in

breast cancer. Thus the combined teachings of Maestro, Rosivatz, and Martin suggest it would be obvious to use Twist gene expression relative to normal controls to determine prognosis. Soritou teaches 56 genes were known to be a bona fide prognostic indicator of breast cancer. Thus is would have been obvious to the artisan to additionally detect Twist gene expression due to the teachings of Martin that twist was known to be more highly expressed in node positive cancers. The artisan would have a reasonable expectation of success as Soritou teaches his combination of gene markers works and the addition of Twist expression for the determination of prognosis would provide additional information on a gene known to be involved in process known to correlate with cancer progression and metastasis.

Summary

No claims are allowed.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Juliet C Switzer/
Primary Examiner, Art Unit 1634